

REMARKS

Claims 18-31 are pending in the above-identified application. All claims stand rejected under 35 U.S.C. § 103(a) for obviousness. In addition, Claims 19 and 25 stand rejected under 35 U.S.C. § 112, second paragraph, for lack of clarity.

With this Reply, Claims 18-20, 22-25, and 29 have been amended to correct various typographical errors and claim dependencies. None of these amendments introduces new matter.

I. Examiner's Request for Copies of Disclosed References

Enclosed with this Reply are copies of the seven following references requested by the Examiner:

1. Jang. "Advanced Polymer Composites." Chapter 1, Introduction, *The Materials Information Society* (to be provided at a later date);
2. Norian Corporation. "The Material Science of Norian SRSTTM Skeletal Repair SystemTM." Product Information Sheet (enclosed herewith as Exhibit A);
3. Rey *et al.* (1996) "Chemical Properties of Poorly Crystalline Apatite." *Phosphorus Res. Bull.* 6:67-70 (enclosed herewith as Exhibit B);
4. Ducheyne *et al.* "Introduction to Bioceramic Composites." *Bioceramics, Advanced Series in Ceramics*, Vol. I (enclosed herewith as Exhibit C);
5. U.S. Patent No. 5,019,379 (Domb *et al.*) (enclosed herewith as Exhibit D);
6. U.S. Patent No. 5,049,157 (Mittelmeier *et al.*) (enclosed herewith as Exhibit E); and
7. U.S. Patent No. 5,264,215 (Nakabayashi *et al.*) (enclosed herewith as Exhibit F).

II. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 19 and 25 have been rejected under 35 U.S.C. §112, second paragraph, for lack of clarity. The Examiner has suggested that “word(s) seem to be missing” from these claims (Office Action, page 2). With this response, claims 19 and 25 have been amended to correct typographical errors and to insert necessary words. In view of these amendments, Applicants respectfully submit that the indefiniteness rejections may now be withdrawn.

III. Rejections Under 35 U.S.C. § 103(a)

Claims 18-31 have been rejected under 35 U.S.C. § 103(a) for obviousness over U.S. Patent No. 5,820,632 to Constantz et al. (hereinafter “Constantz”), in view of U.S. Patent No. 4,429,691 to Niwa et al. (hereinafter “Niwa”) and International Application No. WO 90/00892 to Sugihara et al. (hereinafter “Sugihara”). The Examiner has suggested that it would have been obvious to one of skill in the art to modify the self-hardenable calcium phosphate compositions taught by Constantz “with added components to provide strength, delivery of drugs and/or bone replacement template” as shown by Constantz, Niwa, and Sugihara (Office Action, pages 2-3). Applicants respectfully disagree.

To establish a case of *prima facie* obviousness, the cited references must teach or suggest every claim limitation, and the prior art must provide a motivation to combine the cited references as well as a reasonable expectation of success upon doing so. See, e.g., MPEP § 2142.

Constantz teaches calcium phosphate cement compositions capable of setting to form bone-like materials, such as hydroxyapatite (col. 2, lines 28-43). The cement compositions are formed by combining a calcium source and a phosphoric acid source with a lubricant (e.g., a water, gel, or colloid; col. 3, lines 3-17). Additional materials may, optionally, be included in Constantz's cement compositions (col. 3, line 11). The Examiner has suggested that Constantz specifically teaches the addition of supplemental materials including "bone protein, collagen, matrix protein, [and] the instant decriminalized [*sic*] bone matrix (col. 6, lines 25-35)" (Office Action, page 2).

The passage in Constantz that is relied upon by the Examiner actually reads as follows:

In many situations, a wide variety of additives may be included in the medium to provide for specific properties. One group of additives is protein. Bone associated proteins may be added to modify the physical properties of the composition, enhance resorption, angiogenesis, cell entry and proliferation, mineralization, bone formation, growth of osteoclasts and/or osteoblasts, or the like. Proteins of particular interest are the different types of collagen, particularly Type I. Other proteins include osteonectin, bone sialoproteins (Bsp), alpha-2HS-glycoproteins, bone Gla-protein (Bgp), matrix Gla-protein, bone phosphoglycoprotein, bone phosphoprotein, bone proteoglycan, protolipids, bone morphogenic protein, cartilage induction factor, platelet derived growth factor and skeletal growth factor. Other proteins associated with other parts of human or other mammalian anatomy, include proteins associated with cartilage, such as chondrocalcinizing protein; proteins associated with dentin, such as phosphophoryn, glycoproteins and Gla proteins; or proteins associated with enamel, such as amelognin and enamelin. (col. 6, lines 23-42).

This passage nowhere mentions demineralized bone matrix or suggests that demineralized bone matrix may be added to the disclosed calcium phosphate composition.

In further support of this contention, Applicants have enclosed herewith two (2) scientific publications evidencing that demineralized bone matrix is a material whose composition and properties are distinct from those of the materials identified by Constantz in the above-quoted passage. See Mizuno, S. & Glowacki, J. (1996) "Three-Dimensional Composite of Demineralized Bone Powder and Collagen for *In Vitro* Analysis of Chondroinduction of Human Dermal Fibroblasts." *Biomaterials* 17:1819-1825 (hereinafter "Mizuno;" enclosed herewith as Exhibit G); Spampata, R. et al. (1992) "Accelerated Endochondral Osteoinduction in the Absence of Bone Matrix Particles in a Rat Model System." *J. Oral Maxillofac. Surg.* 50:140-151 (hereinafter "Spampata;" enclosed herewith as Exhibit H). Mizuno teaches an osteogenic collagen/demineralized bone powder (DBP) composite sponge. The collagen facilitates fibroblast entry into the sponge *in vivo*, while the DBP induces bone formation at the implant site (Mizuno, at pages 1820-1823). Spampata teaches that DBP is a complex material including numerous components, such as "collagen, matrix Gla protein, GAGs and proteoglycans, polypeptide growth factors including TGF- β 1 and TGF- β 2, and osteoinductive factors OP-1, BMP-2, osteogenin (BMP-3), and other materials," and concludes it is "difficult to ascribe biological effects to a single agent" (Spampata, at pages 141 & 149). Moreover, Spampata suggests the use of extracted proteins rather than demineralized bone matrix. In fact, Spampata teaches away from the use of demineralized bone matrix by emphasizing the following advantages associated with the use of extracted proteins:

- 1) the avoidance of lengthy and potentially hazardous grinding and sieving of dry bone to a specific particle size, 2) reduction of antigenic, viral, and bacterial components in the implant by eliminating the particulate material, 3) sterilization possibilities for the soluble GE [guanidine-extractable] material through

ultrafiltration, ultraviolet irradiation, ethanol treatment, and 4) ease of storage of active protein at -80°C. (Spampata, at page 150).

In view of these references, Applicants submit that the recitation of supplemental materials in the above-quoted passage from Constantz provides neither a teaching nor a suggestion that demineralized bone matrix may be added to calcium phosphate compositions, as recited in pending Claims 18-31.

Moreover, Niwa and Sugihara cannot remedy the deficiencies of Constantz because neither contains a single mention of demineralized bone matrix, let alone a teaching or suggestion that demineralized bone matrix may be used in calcium phosphate compositions. Niwa discloses apatitic calcium phosphate powders having a crystal size between 50 angstroms and 10 microns (col. 3, line 37 – col. 4, line 36). Sugihara discloses a hardening material including a calcium phosphate powder, a hardening liquid, and collagen or a collagen derivative (page 2, lines 20-25). Applicants note that the Examiner has pointed to no passage in Niwa or Sugihara that discloses the use of demineralized bone matrix (Office Action, page 3).

Thus, none of the cited references teaches or suggests the inclusion of demineralized bone matrix in a calcium phosphate composition – a limitation of rejected Claims 18-31. Applicants respectfully submit that the obviousness rejection of these claims cannot be sustained and, accordingly, request its withdrawal.

CONCLUSION

In view of the foregoing remarks, it is submitted that Claims 18-31 are in condition for allowance, which action is earnestly solicited. The Examiner is invited to contact the undersigned by telephone should any issues remain outstanding.

Applicants note that the Office action was mailed to the incorrect address.

Effective immediately, please address all communication in this application to:

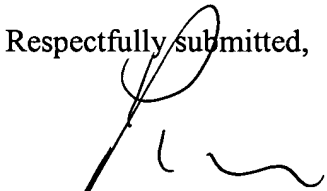
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Enclosed is a petition to extend the period for replying for three months, to and including September 29, 2003, as September 27, 2003 falls on a Saturday, and a check for the fee required under 37 C.F.R. § 1.17(a). If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date:

Sept. 29, 2003



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